

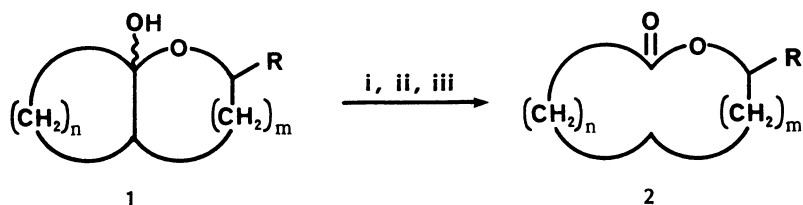
A Simple New Synthesis of Macrolides by a Four Atom Ring Expansion of Cyclic Ketones through a Consecutive Intramolecular Homolytic Addition— $\beta$ -Scission of Alkoxy Radicals. A New Entry to the Synthesis of 15-Pentadecanolide (Exaltolide)<sup>1)</sup>

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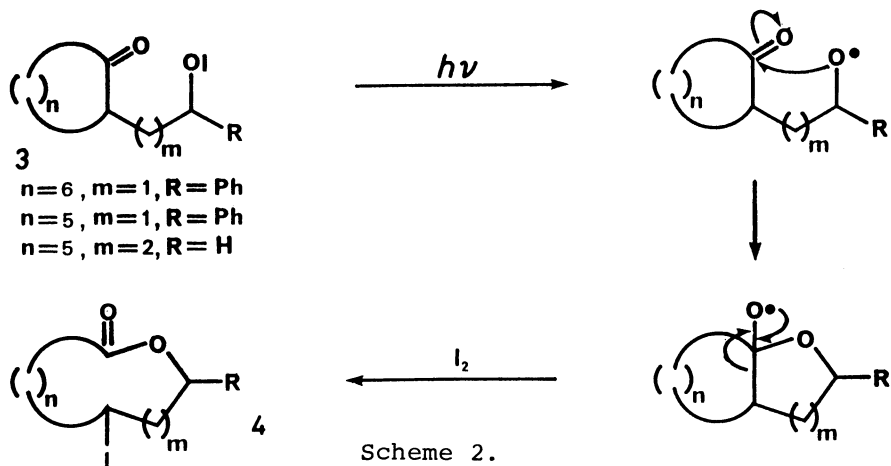
We describe a simple new synthesis of 16-membered macrolide, 15-pentadecanolide, based on a novel four atom ring expansion of cyclic ketones through a consecutive intramolecular homolytic addition— $\beta$ -scission of alkoxy radicals.

We have recently reported a new general synthesis of medium-sized lactones **2** based on a radical-induced  $\beta$ -scission of catacondensed lactols **1** as outlined in Scheme 1.<sup>2)</sup> Utilizing this method, 9 to 11-membered lactones can be efficiently synthesized.



i)  $\text{HgO-I}_2$ -benzene; ii)  $h\nu$ ; iii)  $\text{Bu}_3\text{SnH AIBN-}h\nu$ ;

Scheme 1.



Scheme 2.

During this investigation, we found that lactones **2** are formed in

unexpectedly high yields by the photolysis of the hypiodites of catacondensed lactols 1 in which the equilibria between the lactols 1 and the open-chain hydroxy ketones in solution are almost entirely toward latter. We explained the formation of the lactones in high yields in these cases as due to the formation of a portion of the lactones 4 through an intramolecular addition of the alkoxyl radical (generated from the hypiodite of the open-chain alcohols 3) to the carbonyl group, as outlined in Scheme 2.

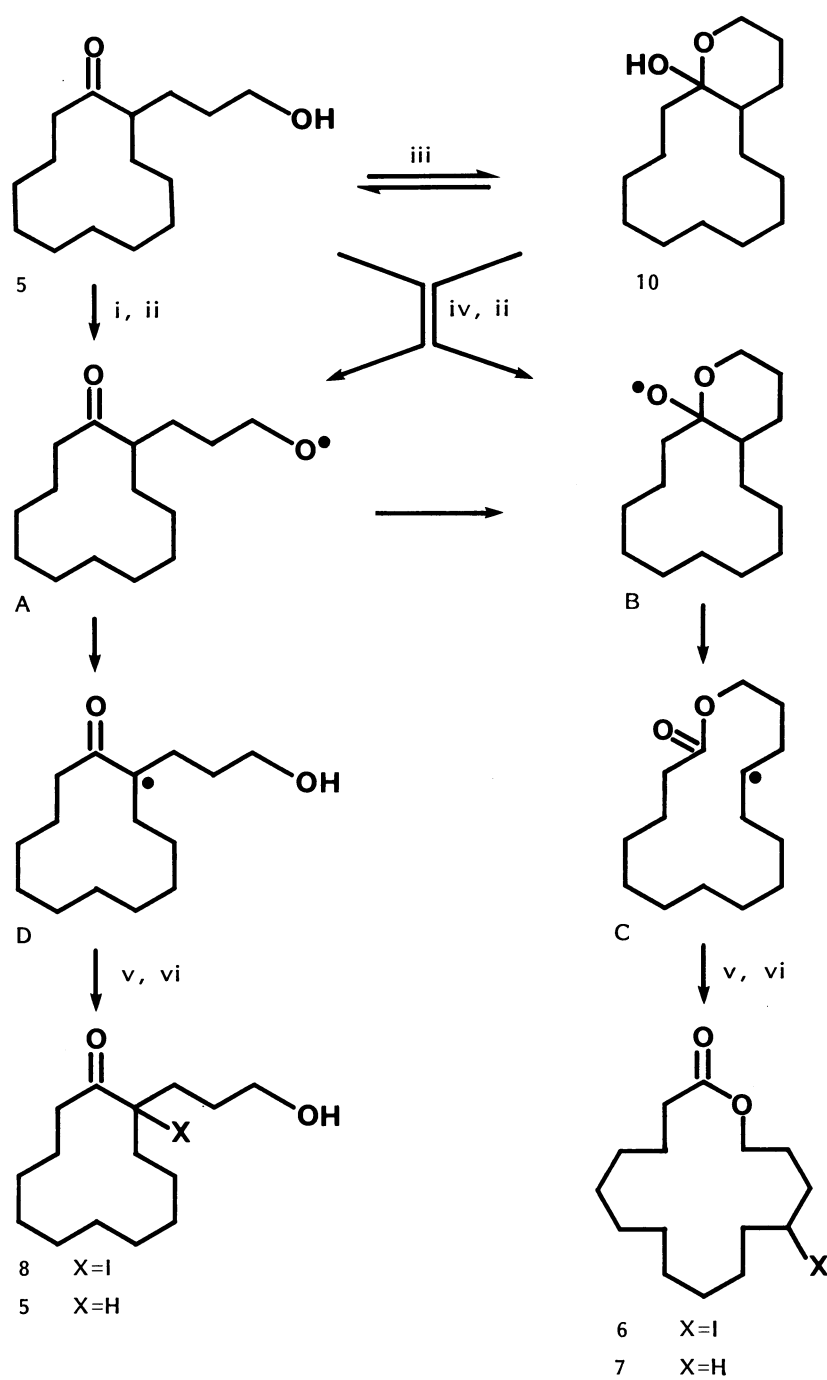
We wish to report here that the assumed process is indeed the case and this new process can be utilized for a simple new synthesis of macrolides by a four atom ring expansion of cyclic ketones.

<sup>1</sup>H NMR spectroscopy showed that with regard to 2-(3'-hydroxypropyl)-cyclododecanone (5),<sup>2)</sup> readily obtainable from a commercially available cyclododecanone, its equilibrium in hexadeuteriobenzene favors hydroxy ketone 5 and lactol (10) was essentially absent in the solution. We also found that the equilibrium was not affected in the additions of iodine and pyridine.

The hydroxy ketone 5 (400 mg) in benzene (60 ml) containing mercury(II) oxide and iodine (3 mol equiv. each) and pyridine (0.6 ml) was placed in a Pyrex vessel and irradiated with a 100-W high pressure Hg arc for 5 h in an atmosphere of nitrogen to yield 12-iodopentadecan-15-olide 6,<sup>3)</sup> (30%) and crystalline 2-iodo-2-(3'-hydroxypropyl)cyclododecanone (8),<sup>4)</sup> (34%), separable by preparative TLC. Irradiation of the benzene solution of 6 containing tributyltin hydride and AIBN gave crystals of 15-pentadecanolide (7)<sup>5)</sup> in 92% yield. Similar treatment of 8 gave the starting hydroxy ketone 5 in 40% yield as outlined in Scheme 3.

Although 15-pentadecanolide has been synthesized by many different methods, e. g. cyclization of  $\omega$ -hydroxy- or halocarboxylic acids and ring expansion,<sup>6-8)</sup> the present new synthesis may perhaps be one of the simplest so far reported.

We then found that the addition of acid to a CDCl<sub>3</sub> solution of hydroxy ketone 5 brought about an appreciable shift of the equilibrium from hydroxy ketone 5 to lactol 10. <sup>1</sup>H NMR spectroscopy showed that approximately 36% and 25% of the lactol 10 is respectively generated when 2-5 equivalents of pyridine hydrochloride or pyridinium p-toluenesulphonate are added to the CDCl<sub>3</sub> solution of hydroxy ketone 5. Irradiation of the equilibrium mixture of 5 and 10 in dichloromethane containing pyridine hydrochloride in the presence of mercury(II) oxide and iodine for 4 h as described above raised the yield of the formation of iodo lactone 6 to 54%.<sup>9)</sup> The paths of the formation of iodo lactone 6 and iodo-hydroxy ketone 8 are outlined in Scheme 3. Iodo lactone 6 is clearly formed through a consecutive homolytic process, an intramolecular homolytic addition of the alkoxyl radical (A) to the carbonyl carbon, followed by a regioselective  $\beta$ -scission of the fused bond of the generated alkoxyl radical (B), to yield a macrocyclic radical (C). The conformation of the species (C) prohibits it from reverting to the cyclic alkoxyl radical (B) and favors the trapping of iodine to yield 6. The increase in the yield of iodo lactone 6 in the presence of acids is explained by assuming the formation of the cyclic alkoxyl radical (B) from both hydroxy ketone 5 and lactol 10.  $\alpha$ -Iodo ketone 8 is formed via a trivial intramolecular hydrogen abstraction through a 6-membered cyclic transition state.



i)  $\text{HgO-I}_2$ -benzene; ii)  $h\nu$ ; iii)  $\text{CH}_2\text{Cl}_2$ -pyridine-HCl;  
 iv)  $\text{HgO-I}_2$ - $\text{CH}_2\text{Cl}_2$ -pyridine-HCl; v)  $\text{I}_2$ ;  
 vi)  $\text{Bu}_3\text{SnH-AIBN-}h\nu$

Scheme 3.

The present ring expansion is of considerable synthetic potential for the simple synthesis of macrolides through the one-step insertion of a  $-O-CH_2CH_2CH_2-$  unit into cyclic ketones as readily available starting materials.

Further investigation of the scope of this novel approach to the synthesis of macrolides is being actively pursued and will be reported in future communication.<sup>10)</sup>

#### References

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- 3) HR-FIMS. Found:  $(M+H)^+$ , 367.1151. Calcd for  $C_{15}H_{28}IO_2$ : M, 367.1135. IR(neat)  $1736\text{ cm}^{-1}$  (lactone C=O);  $^1\text{H NMR}$  ( $CDCl_3$ )  $\delta$  2.32 (2H, br, d,  $J = 6.5$  Hz,  $CH_2CO$ ) and 4.07 - 4.27 (3H, m,  $-CH_2OCO$  and CHI).
- 4) HR-FIMS, Found:  $M^+$ , 366.1093. Calcd for  $C_{15}H_{27}IO_2$ : M, 366.1056. IR(Nujol)  $3416$  (OH) and  $1693\text{ cm}^{-1}$  (C=O);  $^1\text{H NMR}$  ( $CDCl_3$ )  $\delta$  3.00 - 3.11 (2H, m,  $-CH_2CO-$ ) and 3.71 (2H, t,  $J = 5.8$  Hz,  $-CH_2O$ ).
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- 8) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 99, 3867 (1977).
- 9) A poor yield of unstable  $\alpha$ -iodoketone **8** was also obtained.
- 10) Satisfactory analytical and spectral results were obtained for all the compounds described in this paper.

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